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PRINCIPAL INVESTIGATOR: Lawrence O. Hall, Ph.D.

CONTRACTING ORGANIZATION: University of South Florida
Tampa, FL 33620-7900

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6. AUTHOR(S)
Lawrence O. Hall, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of South Florida
Tampa, FL 33620-7900

E-Mail: hall@csee.usf.edu

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An enhanced Web based prototype intelligent agent/expert system for matching breast cancer patients to clinical trials has been built. It allows for cost preferences to be entered. Therefore, the system user can choose to rule patients out of trials as quickly as possible without regard to the cost of tests necessary to do this. A user can choose to have questions appear so that the patient is ruled out of the trial with the minimal set of costs (tests) or can choose some combination of approaches. The system has been tested with 14 protocols and designed for maximal responsiveness and scalability as new protocols are added. The files of 178 former patients have been used to test the accuracy of the system. Additionally, the files of 169 current patients have been tested for eligibility. Patients for each of the protocols were correctly found eligible for one or more trials. We found 160 new matching clinical trials for the 169 current patients. A probable listed prototype system has been developed to reorder questions based on the probability they will determine the patient is ineligible for trial and preliminary experiments have shown up to 13% less questions will be required on average. We have also developed a prototype system to quickly add new clinical trials. This has been successfully used by novices to enter new trials.

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3 Introduction

Increasing the enrollment of patients in clinical trials is important to making progress towards finding more effective treatments for breast cancer. Accrual is complicated by a large number potential studies and the cost and complexity of determining whether a patient meets the necessary eligibility criteria. Under this proposal, we are developing a Web based expert system which can determine the patients eligibility for clinical trials. The expert system is designed to take into account the cost of tests which are required to meet inclusion criteria and acquire information in the most cost-effective way possible.

Additionally, it is important to be able to easily add and remove clinical trials to the system. Trials are continually becoming available, going on suspension or being closed to accrual. Towards this end, we have developed a companion Web based system that enables anyone to simply enter the information required to describe the eligibility/ineligibility criteria for a clinical trial. A newly entered trial/protocol can then be directly included in the Clinical trial assignment expert system with no expert intervention.

Finally, we have worked on methods of utilizing probabilities to order questions so that those most likely to rule patient out of a protocol are first. Recent testing has shown this is effective.

4 Body

In this third-year, we have refined the original prototype to produce version 1.4. We have tested it with data from 187 retrospective patients and approximately 200 more recent patients including some who are currently undergoing treatment. We have extensively tested its ability to order questions associated with tests to save dollar costs on over 300 patients. Table 1 summarizes our matching results on the past and current patients. Patients are only evaluated for trials that are currently enrolling patients. The trial status can change when a trial is put on suspension, closed, brought off suspension, or initiated. It can be seen that the system finds all matches that correspond to trials in which patients have been enrolled. For the current 169 patients for which extensive tests have been done, we found 160 new matches to protocols! This is quite promising for increasing accrual.

The cost savings are shown in Table 2. We show the mean test costs with and without the ordering heuristics. Six clinical trials have incurred selection costs; the heuristics have reduced the costs for four of these trials, and have not affected the costs for the other two trials.

There are now 14 protocols available in the system. At the present time, all breast cancer protocols at the Moffitt Cancer Center which are accruing at least two patients a month are available through our system. We are adding two more protocols that just opened and are accruing patients. Our automated clinical trial updating system continues to allow us to easily add trials to the system [1, 2].

We have created a question ordering system that uses a crude probabilistic heuristic. As patients are tested against the system over time, we can keep a record of how many times each question causes a patient to be classified as ineligible for a protocol. These results will take the form of x out of y times that a question was asked it directly caused a patient to be determined ineligible for protocol z. The value $(\frac{x}{y})_{qp}$ can be treated as the probability that question q will cause a patient to be declared ineligible for protocol p. This value will be reasonably reliable

Table 1: Results of selecting clinical trials for the 187 past patients and 169 current patients. We give the number of trial participants, selected by both the system and Moffitt clinicians, and the number of the other eligible patients, identified by the system.

(a) Results for the 187 past patients.

Clinical Trial	Participants	Other Eligible
10822	10	5
10840	0	19
11072	48	26
11378	4	19
11992	5	6
12100	8	20
12101	20	30

(b) Results for the 169 current patients.

Clinical Trial	Participants	Other Eligible
11132	4	1
11931	2	26
11971	4	0
12100	0	5
12101	11	52
12385	0	19
12601	0	1
12643	16	36
12757	1	3
12775	23	17

Table 2: Cost savings by test reordering.

(a) Results for the 187 past patients.

Clinical Trial	Mean Cost	
	W/O Test Reordering	With Test Reordering
10822	$70	$11
10840	$0	$0
11072	$209	$60
11378	$35	$19
11992	$0	$0
12100	$0	$0
12101	$0	$0

(b) Results for the 169 current patients.

Clinical Trial	Mean Cost	
	W/O Test Reordering	With Test Reordering
11132	$0	$0
11931	$0	$0
11971	$192	$192
12100	$0	$0
12101	$0	$0
12385	$0	$0
12601	$36	$3
12643	$0	$0
12757	$107	$107
12775	$0	$0

after the question has been asked more than 30 times. At that point, it can be used to reorder questions. The question with the highest probability of making a patient ineligible for a trial can be displayed first. By doing this patients will be quickly determined ineligible with a minimum number of questions.

Preliminary experiments have been done which indicate this approach does in fact reduce the number of questions necessary to determine eligibility. Results are shown in Table 3.

We selected 90 patients at random from our list of patients and used their data in experiments. A ten-fold cross validation was carried out, so that the system was trained on 81 patients and the remaining 9 patients were tested using the system. The test was done on six protocols for which 90 patients had been tested. As can be seen in Table 3, the probabilistic system allows approximately 13% less questions to be answered to determine eligibility, on average.

Table 3: Probabilistic question ordering vs. analytic question ordering.

Ten-fold cross validation				
	Average number of questions			
Protocol	Probabilistic System	Analytical System	Difference	Difference %
11931	15.35	18.90	3.55	18.78
12100	13.85	13.95	0.10	0.72
12101	21.65	24.75	3.10	12.53
12521	14.75	19.05	4.30	22.57
12601	13.90	15.70	1.80	11.46
12777	14.40	16.10	1.70	10.56
Average	15.65	18.08	2.43	13.42

Key Research Accomplishments:

- We have enhanced our prototype system to very stable version 1.4. We have corrected cost functionality (mostly by getting the costs of tests correct and determining all tests that are done in the routine care) and tested this successfully.
- Utilizing retrospective patient data and current patient data, it has been found that patients are eligible for multiple protocols/trials. Further, with current patient data we find patients eligible for trials and not put on any trial.
- Extensive testing of cost functionality has been done. We have determined that in many cases there is no possibility of saving costs. However, when it is possible the cost mechanism recommends questions in order that will always allow eligibility to be determined in the minimal cost fashion.
- We have developed a method of determining probabilities that questions will show patients are ineligible for trials. The probabilities are determined empirically while the system is in use. We showed that the use of these probabilities to order questions on a query page will result in the need to answer less questions at all times.

Reportable Outcomes: We have had a paper [3], which is attached, accepted to the 2003 IEEE International Conference on Systems, Man, and Cybernetics. We have a revised journal submission that got reasonably positive reviews undergoing the second round of review. A web prototype of the clinical trial assignment system is available at http://morden.csee.usf.edu/moffit with password available from the principal investigator.

5 Conclusions

We have developed a scalable prototype which currently can determine eligibility for fourteen breast cancer clinical trials. The system has been tested using retrospective data from 187 patients who are assigned to some clinical trial and more recently active patients numbering 169. The system correctly finds cases in which a patient is eligible for multiple clinical trials. It has found 160 matching trials for the 169 current patients. This indicates that it is quite likely they use of the system will significantly increase accruals to trials.

The system is able to utilize monetary cost in requesting tests to rule in/rule out a patient from the set of available clinical trials. The default ordering of questions allows the system user to rapidly determine the eligibility or ineligibility of a patient for any subset of the available clinical trials entered into the system. We have been able to show a good average cost saving by using the cost feature to order questions. Of course, there is no guarantee that a clinician would order tests as suggested by the question ordering of our system. However, the potential for cost savings is significant.

The system is Web based and password protected. It provides rapid response when a person enters answers to one or more questions on a page of system selected questions. It can be used from any computer on the World Wide Web. Hence, community physicians will be able to determine the potential eligibility (they may not wish to run all tests) of the patient for clinical trials at cancer centers in their region.

A prototype to enable physicians, nurses or technicians to enter new protocols has been completed. The system is now in use. It reduces the time required to add a new trial or protocol to approximately 1 hour. It enables non-computer scientists to add trial/protocols to the system. This knowledge acquisition tool has been designed to minimize/eliminate the cases where similar questions acquiring essentially the same information would have to be asked. This feature has the potential to cause slight changes to the wording of inclusion/exclusion criteria. We believe that this change is minor and will have no effect on IRB approval.

Last year, we intended to evaluate whether IRB approval would be affected. However, institutional issues prevented this. However, this year we will have new protocols entered using existing questions and plan to go back to the IRB board to discuss any changes in criteria wording to fit existing questions within the system. An example would be a protocol in which there are two questions which ask "is a test value is greater than some threshold" and then a separate question that asks if it is less than some threshold, versus a single question which asks if a test is in some range. We believe that such a change is trivial, but this must be addressed in practice and we will evaluate whether it causes review board decisions to potentially change.

APPENDIX COVER SHEET

Experiments on the Automated Selection of Patients for Clinical Trials

Eugene Fink eugene@csee.usf.edu
Lawrence O. Hall hall@csee.usf.edu
Dmitry B. Goldgof goldgof@csee.usf.edu
Bhavesh D. Goswami bgoswami@csee.usf.edu
Matthew Boonstra boonstra@csee.usf.edu
Jeffrey P. Krischer jpkrischer@moffitt.usf.edu

Computer Science and Engineering, University of South Florida, Tampa, Florida 33620

Abstract – *When clinicians test a new treatment procedure, they need to recruit patients with appropriate medical conditions. We have developed an expert system that helps clinicians to select patients for experimental treatments, and to reduce the cost of related medical tests. We describe experiments on selection of patients for new treatments at the Moffitt Cancer Center.*[1]

Keywords: Medical expert systems, breast cancer, cost reduction.

1 Introduction

When clinicians conduct treatment experiments, called *clinical trials,* they have to recruit participants among current patients. To select prospective participants, clinicians analyze the data of available patients, which has traditionally been a manual process. Studies have shown that clinicians miss up to 60% of the eligible patients, which delays the completion of clinical trials.

To address this problem, researchers built several systems that helped clinicians to select trial participants. Ohno-Machado *et al.* [1993] developed the AIDS[2] system, which selected AIDS patients for clinical trials. Musen *et al.* [1996] built a rule-based system, called EON, that also assigned AIDS patients to clinical trials. Bouaud *et al.* [1998; 2000] created the ONCODOC system, which suggested trials for cancer patients. Séroussi *et al.* [1999; 2001a; 2001b] used ONCODOC to select trial participants at two hospitals, which helped to increase the number of selected patients by a factor of three.

The National Cancer Institute has created a search engine for selection of clinical trials, available through the Internet at *www.cancer.gov/search/clinical_trials.* It prompts a user to answer several questions about a patient, and gives a list of potentially matching trials; however, it does not determine whether the patient satisfies all requirements for these trials.

Fallowfield *et al.* [1997] studied how physicians selected cancer patients for clinical trials, and compared manual and automated selection. They showed that expert systems could improve the selection accuracy, but physicians were reluctant to use these systems. Carlson *et al.* [1995] conducted similar studies with AIDS trials, and also concluded that expert systems could lead to a more accurate selection.

A recent project at the University of South Florida has also been aimed at automated identification of prospective trial participants. Theocharous developed a Bayesian system that selected clinical trials for cancer patients [Theocharous, 1996; Papaconstantinou *et al.*, 1998], and Bhanja *et al.* [1998] built a qualitative rule-based system for the same task.

We have continued their work, built a new version of the rule-based system [Kokku *et al.*, 2002; Nikiforou *et al.*, 2002; Nikiforou, 2002], and applied it to selection of patients for breast-cancer trials at the Moffitt Cancer Center, located on campus of the University of South Florida. We outline the design of this system and present an empirical evaluation of its effectiveness.

2 Knowledge base

Physicians at the Moffitt Cancer Center conduct about 150 clinical trials. We have developed an expert system that helps clinicians to select trials for eligible patients; it consists of a knowledge base and web-based interface for entering patient data. The knowledge base contains information about related medical tests, as well as logical expressions that determine a patient's eligibility for each trial. The description of a medical test includes its dollar cost and list of questions that can

[1] 0-7803-7952-7/03/$17.00 © 2003 IEEE.

(a) TESTS AND QUESTIONS

General information
What is the patient's sex?
What is the patient's age?

Mammogram, Cost is $150
What is the cancer stage?
Does the patient have invasive cancer?

Biopsy, Cost is $400
How many lymph nodes have tumor cells?
What is the greatest tumor diameter?

Electrocardiogram, Cost is $200
Does the patient have cardiac arrhythmias?

(b) ELIGIBILITY CRITERIA

sex = FEMALE and
age $\leq$ 45 and
cancer-stage $\in$ {II, III} and
invasive-cancer = NO and
lymph-nodes $\leq$ 3 and
(*arrhythmias* = NO or
tumor-diameter $\leq$ 2.5)

Figure 1: Description of medical tests and trial-eligibility criteria in the trial-selection system.

be answered based on the test results (Figure 1a). The trial-eligibility criteria are a logical expression, which includes variables that represent the patient data, as well as equalities, inequalities, "set-element" relations, conjunctions, and disjunctions (Figure 1b).

The system collects data until it can determine whether the eligibility expression is TRUE or FALSE. For example, if a clinician uses the system to determine a patient's eligibility for the trial in Figure 1(b), it first asks about the patient's sex and age. If the patient satisfies the corresponding conditions, the system asks for the mammogram results, and then requests the biopsy and electrocardiogram data. The ordering of tests depends on their costs and on the amount of information provided by test results. The system begins with the mammogram because it is cheaper than the other tests and provides data for two clauses of the eligibility expression.

3 Selection of participants

We have built a knowledge base for the breast-cancer trials at the Moffitt Cancer Center, including five completed trials and ten current trials. We have applied the system to retrospective data from 187 past patients and 169 current patients, and compared the results with the manual selection by Moffitt clinicians. The system has identified all eligible patients for each trial, whereas the clinicians have selected about half of the eligible patients. We summarize the results for the past patients in Table 1(a), and the results for the current patients in Table 1(b). The "participants" column shows the number of actual participants of each trial; the "other eligible" column gives the number of the other eligible patients identified by the system.

For every current patient who has not participated in a matching trial, we have checked whether she participated in any other trial, and we show the results in Table 2. We have not done a similar analysis for the past patients because of insufficient data. The "incompatible" column in Table 2 includes the number of eligible patients who skipped a specified trial because of participation in another incompatible trial. The "compatible" column shows the number of patients who participated in another compatible trial, and could also have participated in the specified trial. Finally, the "no other trial" column gives the number of eligible patients who have not participated in any trial.

The results show that the system can identify eligible patients who have not been selected by clinicians; thus, it can increase the number of trial participants. For the patients in the reported experiments, it could increase the number of participants by a factor of two.

4 Cost reduction

If the patient records do not provide enough data, clinicians perform medical tests as part of the selection process. They can reduce the overall test cost by first requiring inexpensive tests, and then using their results to avoid some expensive tests.

The developed system suggests the ordering of tests that reduces their expected cost. After getting the results of the first test, it re-evaluates the need for the other tests and revises their ordering. The choice of the first test is based on three criteria. The system scores all required tests according to these criteria, computes a linear combination of the three scores for every test, and chooses the test with the highest score.

1. *Cost of a test.* The system gives preference to less expensive tests.
2. *Immediate decision.* If a test can lead to immediate acceptance or rejection of the trial, the system prefers it to other tests.
3. *Number of related clauses.* The system prefers the tests that provide data for the largest number of clauses in the eligibility expression.

The system disregards the costs of tests performed in the normal course of treatment, and accounts only for the costs related to the trial selection. For example, if a patient needs a mammogram regardless of clinical-trial participation, the system views it as a zero-cost test. On the other hand, if the only purpose of the biopsy and electrocardiogram is to select clinical trials, the system uses heuristics to order these tests.

Table 1: Results of selecting trials for 187 past patients and 169 current patients. We give the number of trial participants, selected by both the system and Moffitt clinicians, and the number of the other eligible patients, identified by the system.

(a) Results for the 187 past patients.

Clinical Trial	Participants	Other Eligible
10822	10	5
10840	0	19
11072	48	26
11378	4	19
11992	5	6
12100	8	20
12101	20	30

(b) Results for the 169 current patients.

Clinical Trial	Participants	Other Eligible
11132	4	1
11931	2	26
11971	4	0
12100	0	5
12101	11	52
12385	0	19
12601	0	1
12643	16	36
12757	1	3
12775	23	17

Table 2: Participation of the patients who skipped a matching trial in other trials. We show the number of patients who skipped the trial because of participation in another incompatible trial; the number of patients who were on another trial compatible with the skipped trial; and the number of eligible patients who were not on any trial.

Clinical Trial	Incompatible	Compatible	No Other Trial
11132	0	1	0
11931	0	11	15
11971	0	0	0
12100	0	1	4
12101	13	6	33
12385	8	2	9
12601	0	0	1
12643	0	10	26
12757	0	1	2
12775	3	3	11

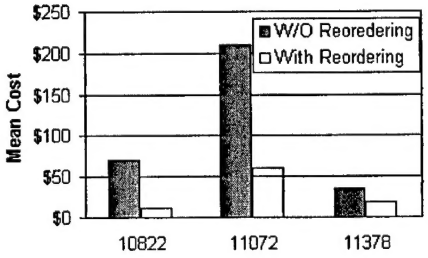
Table 3: Cost savings by test reordering.

(a) Results for the 187 past patients.

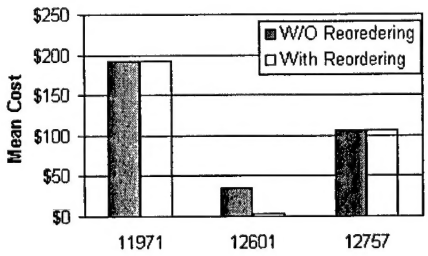
Clinical Trial	Mean Cost	
	Without Test Reordering	With Test Reordering
10822	$70	$11
10840	$0	$0
11072	$209	$60
11378	$35	$19
11992	$0	$0
12100	$0	$0
12101	$0	$0

(b) Results for the 169 current patients.

Clinical Trial	Mean Cost	
	Without Test Reordering	With Test Reordering
11132	$0	$0
11931	$0	$0
11971	$192	$192
12100	$0	$0
12101	$0	$0
12385	$0	$0
12601	$36	$3
12643	$0	$0
12757	$107	$107
12775	$0	$0



(a) Results for the 187 past patients.



(b) Results for the 169 current patients.

Figure 2: Costs with and without test reordering. We plot the results for the six trials that have incurred nonzero selection costs.

We show the mean test costs with and without the ordering heuristics in Table 3, and give a graphical view of the cost savings in Figure 2. The results confirm that the heuristics reduce the cost of the selection process. Six clinical trials have incurred selection costs; the heuristics have reduced the costs for four of these trials, and have not affected the cost for the other two trial.

The results in Table 3(a) differ from similar experiments with an earlier version of the system, reported in the article by Kokku *et al.* [2002], because of two changes in the system. First, the current version disregards the costs of the tests required for the regular treatment, which do not affect the trial-selection expenses, whereas the earlier version counted all costs. Second, some costs in the old system were out-of-date, and we have corrected them based on the data from the Moffitt accounting department.

5 Concluding remarks

We have developed an expert system that selects clinical trials for eligible patients. Experiments have confirmed that the system has the potential to improve the accuracy of selecting trial participants. They have also shown that the ordering of medical tests affects their overall cost, and the implemented heuristics reduce the cost of finding trial participants.

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